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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/155,739	09/11/1998	MARY M. BENDIG	15270-001430	9068

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Teresa Stanek Rea, ESQ
Burns Doane Swecker & Mathis, LLP
1737 King Street, Suite 500
Alexandria, VA 22314

EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/155,739	BENDIG ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 18-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 18-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.
Applicant's submission filed on 7/14/03 has been entered.

Claims 1 and 18-27 as it reads on the election of rheumatoid arthritis are under consideration in the instant application.

Claims 2-17 have been canceled previously.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 7/14/03.
The rejections of record can be found in the previous Office Actions.

3. Again, it is noted that a number of pages in the specifications have faint or missing words.

Applicant may consider providing a substitute specification or may consider discussing the issue with the examiner in order to correct the deficiencies in the specification.

If a substitute specification is submitted to correct the numerous entries to be amended in the specification, then the substitute specification filed must be accompanied by a statement that it contains no new matter. Such statement must be a verified statement if made by a person not registered to practice before the Office.

As noted by applicant's amendment, filed 7/14/03; this objection will be held in abeyance until there is an indication of allowable subject matter.

4. Applicant's amendment of the first line of the specification to indicate priority is acknowledged.

Applicant submits that the instant claims the benefit of, at least, the 11/21/95 priority filing date, which is the filing date of USN 08/561,521, now U.S. Patent No. 5,840,299. Applicant relies upon the disclosure therein of methods of using the 21.6 monoclinal antibody to block α4-dependent interactions of the VLA-4 receptor, including the treating of rheumatoid arthritis.

However, USSN 08/561,521, now U.S. Patent No. 5,840,299 does not appear to provide sufficient written support for the disclosure of methods of using the humanized 21.6 antibody for "manufacturing a medicament for treating rheumatoid arthritis".

Applicant has not provided sufficient documentary support for the written description of "manufacturing a medicament for treating rheumatoid arthritis" in USSN 08/561,521, now U.S. Patent No. 5,840,299.

It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

Therefore, the filing date of the instant claims is deemed to be the filing date of the priority application PCT US96/18807, filed 11/21/96, as the earlier priority applications do not provide written support for "manufacturing a medicament for treating rheumatoid arthritis" (as well as the other non-elected diseases), and thus does not support the claimed limitations of the instant application.

5. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 C.F.R. § 1.75(d)(1) and M.P.E.P. § 608.01(l). Correction of the following is required:

Upon a review of the instant specification, it does not appear that the instant specification provides sufficient written description of:

" A method of using a humanized antibody to alpha-4 integrin in the manufacture of a medicament for treating rheumatoid arthritis, ..." See claim 1.

While the specification discloses "pharmaceutical compositions" and "methods of treating rheumatoid arthritis" (pages 23-31, Pharmaceutical Compositions and Methods of Treatment), the disclosure of the term "medicament" is not readily apparent in the specification as filed. In addition, methods of "manufacturing a medicament" is not readily in the specification as filed. It appears that the written support for the instant claims relies upon the original claims only.

Applicant should amend the specification to provide sufficient antecedent basis for the written description of the instant claims.

6. Claims 1 and 18-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 18-26 are indefinite in their recitation as methods because the methods do not clearly set forth method steps and there is an absence of a resolution step, which reads back on the preamble of the claimed methods. The claims are indefinite because they merely recited a use without any active, positive steps delimiting how this use is actually practiced. Ex parte Erlich, 3 USPQ2d 1011 (CPAI 1986). See MPEP 2173.05(q).

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1 and 18-27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wayner et al. (U.S. Patent No. 5,730,978) in view of Bendig et al. (WO 95/19790;IDS, #10) essentially for the reasons of record set forth in the previous Office Actions.

Applicant's arguments, filed 7/14/03, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

Applicant traverses this rejection for the reasons previously set forth in the Amendment and Reply dated 10/17/01; however, it is unclear what communication is being relied upon, given that no paper in this file application is dated 10/17/01.

Applicant's comments on the criteria of obviousness are acknowledged.

Applicant asserts that the prior art fails to teach or suggest the treatment of rheumatoid arthritis as well as the use of the particular humanized 21.6 antibody to treat rheumatoid arthritis.

Again, applicant's comments, including the reliance upon Bergsteinsdottier et al. (J. Immunol. 164: 1564-1568, 2000), Kuby et al. (Immunology, Chapter 20: Autoimmunity, pages 477-492, W.H. Freeman and Co. 1998), Corthay et al. (International Immunology 11: 1065-1073, 1999), Saidq et al. (Merritt's Textbook of Neurology, Chapter 128: Demyelinating Diseases. Pp 804-829, Rowland ed., Williams and Wilkins, Baltimore, 1995), and El-Gabalawy et al. (Arthritis Res. 4 (suppl 3): S297-S301, 2002) concerning the divergent etiologies and symptoms of multiple sclerosis and rheumatoid arthritis are acknowledged.

Again, it should be noted that these references mainly address the differences in the genetic underpinnings of the multiple sclerosis and rheumatoid arthritis as well as the role of γδ T cells and not the commonality of targeting α4 to inhibit the inflammatory response associated with both diseases, taught by the prior art and disclosed in the instant specification as well.

Further, it is noted that it was known in the art that pathogenic and protective roles have been ascribed to Th1 cells in inflammatory autoimmune diseases such as multiple sclerosis, diabetes and rheumatoid arthritis, as evidenced by Lafaille et al. (J. Exp. Med. 186: 307-312, 1997) (see Introduction). It is acknowledged that EAE is a demyelinating disease of the central nervous system widely used as an animal model for multiple sclerosis. Experimental models of autoimmune diseases can rely upon the induction by immunization with specific tissues, such that basic myelin protein is employed for EAE and collagen is employed for arthritis, as evidenced by van Bekkum (J. Clin. Immunol. 20: 10-16, 2000).

Applicant asserts that Lafaille et al. and Bekkum et al. are irrelevant to an obviousness analysis, since they post-date the time of the claimed invention.

In certain circumstances, references cited to show a universal fact need not be available as prior art before applicant's filing date. Later publications showing factual evidence cen be cited in situations where the facts shown in the reference are evidence that as of applicant's filing date.

Applicant also asserts that both Lafaille et al. and Bekkum et al. supports the position that EAE is not predictive model for rheumatoid arthritis.

Applicant provides Yednock et al. (Nature 356: 63-66, 1992), Fischer et al. (Scand. J. Immunol. 38: 158-166, 1993), Issekutz et al. (Clin. Immunol. Immunopathol. 67: 257-263, 1993) and Issekutz et al. (J. Exp. Med. 181: 1197-1203, 1995) to indicated that the state of the art at the time the invention was made that no support for the notion that inhibition of α4 integrin by a humanized antibody would provide a therapeutic effect against rheumatoid arthritis.

While the etiologies of the autoimmune diseases and experimental models of autoimmune diseases do have different etiologies, the prior art, as well as applicant's disclosure recognized that the ordinary artisan could target inflammatory mediators (e.g. cells) associated with these conditions in order to treat these conditions with an expectation of success at the time the invention was made. Again, it is noted that Wayner et al. does teach targeting a number of inflammatory or autoimmune conditions, including rheumatoid arthritis. In addition, given that the teachings of Bendig et al. to treat the highly difficult case of multiple sclerosis, the ordinary artisan would have had a reasonable expectation of success in treating other autoimmune conditions such as rheumatoid arthritis.

Also, it is noted that Example 9 of the instant specification discloses the efficacy of the humanized 21.6 antibody in the prophylactic and therapeutic treatment of EAE in an animal model simulating multiple sclerosis in humans. Therefore, applicant has relied upon experimental models of treating EAE to support the ability of the humanized 21.6 antibody to treat autoimmune diseases encompassing rheumatoid arthritis as well as multiple sclerosis (also, see Section VII, Methods of Treatment on pages 25-31 of the instant specification).

In addition, the Background of the Invention of the instant specification is consistent with the prior art that $\alpha 4$ is a therapeutic target to treat pathologic inflammation by inhibiting over-responsive leukocytes. It is noted that Wayner et al. discloses a number of diseases including autoimmune diseases such as rheumatoid arthritis and multiple sclerosis with a common mode of action to Bendig et al. as well as the instant application.

Again, applicant has not addressed the clear teachings of the prior art drawn to inhibiting deleterious inflammation by targeting leukocytes with $\alpha 4$ -specific antibodies to treat a number of inflammatory and autoimmune conditions, which is consistent with the same mode of action relied upon by the instant disclosure.

Again, applicant fails to address the clear teachings of the prior art of both Wayner et al. and Bendig et al. of inhibiting the inflammatory responses in autoimmune responses with $\alpha 4$-specific antibodies, including rheumatoid arthritis and the particular humanized 21.6 antibody of the claimed invention

A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." See In re Gurley , 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

Here in contrast to applicant's assertions of teaching away by the prior art provide by applicant, there is no discouragement nor skepticism in the prior art employed in the rejection under 35 USC 103 itself for inhibiting the inflammatory responses in autoimmune responses with $\alpha 4$-specific antibodies, including rheumatoid arthritis and the particular humanized 21.6 antibody of the claimed invention

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). In this case the teachings of both Wayner et al. and Bendig et al. teach inhibiting the inflammatory responses in autoimmune responses with α4-specific antibodies, including rheumatoid arthritis and the particular humanized 21.6 antibody of the claimed invention and the teachings of both Wayner et al. and Bendig et al. teach and claim success in treating inflammatory conditions to solve the same or nearly the same problems of pathologic inflammation in inflammatory and autoimmune conditions by targeting leukocytes with α4-specific antibodies would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art.

The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144

In addition with respect to claims 1 and 18-26, it is noted that applicant's arguments are directed to a recitation of the intended use of the claimed invention as it reads on a "method of using a humanized antibody in the manufacture of a medicament for treating rheumatoid arthritis". Applicant is reminded that the claims are drawn to manufacturing a medicament not drawn to a method of treating arthritis. The recitation of "for treating rheumatoid arthritis" is a recitation of intended use of the medicament comprising humanized α4-specific antibodies. Applicant has not distinguish the claimed invention from the prior art. Also, it is noted that the instant specification, including priority documents, If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See In re Casey, 152 USPQ 235 (CCPA 1967) and In re Otto, 136 USPQ 458, 459 (CCPA 1963).

Applicant's arguments are not found persuasive.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

After January 20, 2004, Phillip Gambel's telephone number will be (571) 272-0844 and Christina Chan's telephone Number will be (571) 272-0841.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
November 24, 2003